



EDITORIAL

HIGH SPECIFICITY MAKES DNA SCREENING THE METHOD OF CHOICE FOR DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLAEMIA

The diagnosis of familial hypercholesterolaemia (FH) is based on clinical findings, a family history of premature atherosclerosis and elevated plasma cholesterol levels.¹ Identification of heterozygous FH is complicated by the fact that biochemical parameters may overlap between normal and affected individuals, especially in children,² and most adult patients do not present with cholesterol deposits in the skin and tendons. The importance of a DNA test that can provide a simple yes/no answer has now been demonstrated clearly in the article by Vergotine and colleagues in this issue of the *Journal*.³ Mutation screening of the low-density lipoprotein receptor (LDLR) gene in more than 1 000 subjects has shown that 15.6% of at-risk family members may be misdiagnosed when total cholesterol (TC) concentration at the 80th percentile for age and gender is used as a biochemical cut-off point for a diagnosis of FH, compared with 12.4% using the 95th percentile. The sensitivity and specificity of FH diagnosis according to TC values (80th percentile) were shown to be 89.3% and 81.9%, respectively.

The main advantage of DNA testing for FH is its very high specificity compared with clinical criteria. Specificity of a test is defined as the ability to identify positively only those individuals who have the disease, in order to avoid treatment of unaffected individuals. The test should also be sensitive enough to avoid missing the diagnosis and subsequent treatment of affected individuals. Recent surveys have shown that the majority of the estimated 10 million people affected with FH worldwide are undiagnosed, untreated or poorly treated. Only a small percentage (~2.5%) of the estimated 120 000 FH heterozygotes in South Africa have been identified and of the expected 200 homozygotes, less than 100 patients have been diagnosed as having FH.⁴

To date, more than 700 LDLR gene mutations underlying FH have been identified worldwide (<http://www.ucl.ac.uk/fh>; <http://umd.necker.fr>), which complicates DNA diagnosis. However, in the South African population where a small number of disease-related mutations predominate,^{5,6} mostly owing to founder effects and/or multiple entries of defective genes into the local population, cost-effective DNA diagnosis is possible. The issue of costs involved in DNA screening is becoming increasingly important in health care systems and

therefore it is advantageous that a DNA test needs to be done only once in a lifetime.

The question may be asked why it is important to distinguish FH from other types of hyperlipidaemias. The main reason is that FH patients have a significantly higher risk of coronary heart disease compared with other hypercholesterolaemics in the general population, and FH requires more aggressive treatment. Coronary deaths occur in 50% of men by the age of 60 years (75% present with coronary symptoms) and only 20% reach the age of 70 years. In women these figures are 15% (45% present with coronary symptoms) and 70%, respectively (Report on a World Health Organisation Consultation on Familial Hypercholesterolaemia, Paris, 3 October 1997). A DNA test for FH furthermore provides a definitive tool for family tracing, allowing accurate disease diagnosis in approximately half of the relatives analysed and consequently preventive treatment.¹⁰ Since most people are in favour of family screening for treatable genetic diseases like FH,¹¹ programmes for systematic DNA screening should be encouraged. However, in order to limit negative reactions the diagnosis should be accompanied by individual counselling on risk and treatment possibilities. Patients should be informed of ethical issues before genetic testing and give their full consent,¹² especially since the identification of an FH-related mutation would affect other relatives who should be made aware of the availability of a genetic test for accurate disease diagnosis in the family.

Maritha J Kotze

Division of Human Genetics
University of Stellenbosch
Tygerberg, W Cape

1. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic Basis of Inherited Disease*. New York: McGraw-Hill, 1995: 1981-2030.
2. Kotze MJ, Peeters AV, Loubser O, et al. Familial hypercholesterolemia: Potential diagnostic value of mutation screening in a pediatric population of South Africa. *Clin Genet* 1998; **54**: 74-78.
3. Vergotine J, Thiar R, Kotze MJ. Clinical versus molecular diagnosis of heterozygous familial hypercholesterolaemia in the South African population. *S Afr Med J* 2001; **91**: 1053-1059 (this issue).
4. Kotze MJ, Marais AD, Raal FJ. Focus on South Africa: MED-PED FH in South Africa. *FH Update: Newsletter on the Diagnosis and Treatment of Familial Hypercholesterolaemia* 1998; **3**: 1-8.
5. Kotze MJ, Langenhoven E, Warnich L, Du Plessis L, Retief AE. The molecular basis and diagnosis of familial hypercholesterolaemia in South African Afrikaners. *Ann Hum Genet* 1991; **55**: 115-121.
6. Meiner V, Landsberger D, Berkman N, et al. A common Lithuanian mutation causing familial hypercholesterolaemia in Ashkenazi Jews. *Am J Hum Genet* 1991; **49**: 443-449.
7. Kotze MJ, Loubser O, Thiar R, et al. CpG hotspot mutations at the LDL receptor locus are a frequent cause of familial hypercholesterolemia among South African Indians. *Clin Genet* 1997; **51**: 394-398.
8. Loubser O, Marais AD, Kotze MJ, et al. Founder mutations in the LDL receptor gene contribute significantly to the familial hypercholesterolemia phenotype in the indigenous South African population of mixed ancestry. *Clin Genet* 1999; **55**: 340-345.
9. Thiar R, Scholtz CL, Vergotine J, et al. Predominance of a 6-bp deletion in exon 2 of the LDL receptor gene in Africans with familial hypercholesterolaemia. *J Med Genet* 2000; **37**: 514-519.
10. Kastelein JJP. Screening for familial hypercholesterolaemia: Effective, safe treatments and DNA testing make screening attractive. *BMJ* 2000; **321**: 1483-1484.
11. Andersen LK, Jensen HK, Juul S, Faergeman O. Patient's attitude toward detection of heterozygous familial hypercholesterolaemia. *Arch Intern Med* 1997; **157**: 553-560.
12. Humphries SE, Galton D, Nicholls P. Genetic testing for familial hypercholesterolaemia: practical and ethical issues. *QJM* 1997; **90**: 169-181.